

Pharmacokinetics of Cefepime in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis

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The pharmacokinetics of cefepime were studied in 10 male patients receiving continuous ambulatory peritoneal dialysis therapy. Five patients received a single 1,000-mg dose and the other five received a single 2,000-mg dose; all doses were given as 30-min intravenous infusions. Serial plasma, urine, and peritoneal dialysate samples were collected; and the concentrations of cefepime in these fluids were measured over 72 h by using a high-performance liquid chromatographic assay with UV detection. Pharmacokinetic parameters were calculated by noncompartmental methods. The peak concentrations in plasma and the areas under the plasma concentration-versus-time curve for the 2,000-mg dose group were twice as high as those observed for the 1,000-mg dose group. The elimination half-life of cefepime was about 18 h and was independent of the dose. The steady-state volume of distribution was about 22 liters, and values for the 1,000- and 2,000-mg doses were not significantly different. The values for total body clearance and peritoneal dialysis clearance were about 15 and 4 ml/min, respectively. No dose dependency was observed for the clearance estimates. Over the 72-h sampling period, about 26% of the dose was excreted intact into the peritoneal dialysis fluid. For 48 h postdose, mean concentrations of cefepime in dialysate at the end of each dialysis interval exceeded the reported MICs for 90% of bacteria which commonly cause peritonitis resulting from continuous peritoneal dialysis. A parenteral dose of 1,000 or 2,000 mg of cefepime every 48 h would maintain the antibiotic levels in plasma and peritoneal fluid above the MICs for 90% of the most susceptible bacteria for the treatment of systemic and intraperitoneal infections.

Cefepime (BM-28142) is a new parenteral cephalosporin antibiotic with a broad antibacterial spectrum (7, 13) and a low affinity for chromosomally mediated β -lactamases (17, 22). Clinical experience indicates that cefepime is safe and well tolerated. The pharmacokinetic properties of cefepime are well documented (1, 2, 4-6). In normal male subjects, cefepime has a mean elimination half-life ($t_{1/2}$) of about 2.2 h and obeys linear kinetics over an intravenous dose range of 250 to 2,000 mg (1, 2). Over 85% of the administered dose is recovered in urine as intact cefepime in subjects with normal kidney function (5). The safety, tolerance, and pharmacokinetics of cefepime have been evaluated in patients with renal impairment, including those on hemodialysis, and dosing regimen adjustments have been developed (4).

Continuous ambulatory peritoneal dialysis (CAPD) is a self-dialysis procedure which is widely recommended as an alternative to hemodialysis in the treatment of end-stage renal disease (15, 18). However, peritonitis is a major and often serious complication of CAPD. Approximately 60% of patients undergoing CAPD develop peritonitis within the first year of the initiation of dialysis (16). Bacterial peritonitis is generally caused by catheter contamination by common skin organisms. The antibacterial spectrum of cefepime covers the bacteria known to cause CAPD-induced peritonitis (16, 21). In light of its excellent antimicrobial characteristics, cefepime is a useful addition to the armamentarium for the treatment of peritonitis and other systemic infections in patients undergoing CAPD.

This study was designed to characterize the safety, toler-

ance, and pharmacokinetic characteristics of cefepime and to investigate the extent of peritoneal cavity entry of cefepime following intravenous administration of single 1,000- and 2,000-mg doses to patients undergoing CAPD. Another objective was to develop a dosage schedule for the use of intravenous cefepime in patients undergoing CAPD.

MATERIALS AND METHODS

Patients. A total of 10 patients undergoing CAPD who did not have evidence of peritonitis and who had no known hypersensitivity to β -lactam antibiotics participated in the study after signing an informed consent form. This protocol was approved by the Committee for the Protection of the Rights of Human Subjects of the Medical School of the University of North Carolina at Chapel Hill. The patients had a mean \pm standard deviation age of 56 ± 11 years, a mean body weight of 78 ± 15 kg, and a mean height of 176 ± 5 cm. The creatinine clearance (CL_{CR}) values for seven patients were less than 0.52 ml/min. The remaining three patients had CL_{CR} values of 1.77, 2.21, and 3.44 ml/min. None of the patients had experienced peritonitis in the 1-month period prior to entry into the study. A physical examination and a laboratory screening profile were performed on each patient before and after the study. All patients had normal liver functions, as determined by routine laboratory liver function tests, and hematologic profiles were normal except for the anemia resulting from chronic renal failure. The patients were not allowed to take any medication unless it was approved by the principal investigator. Beverages containing alcohol or caffeine also were not permitted during the confinement period in the General

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Clinical Research Center of the University of North Carolina, which began at least 12 h prior to dosing and which ended 96 h after dosing. The patients were randomly assigned to the 1,000- or 2,000-mg dose group. There were five patients in each dose group.

Each patient had a long-term indwelling catheter. The CAPD exchange schedule for each patient was 2 liters of 2.5% glucose peritoneal dialysis solution (Dianeal; Travenol Laboratories, Inc., Deerfield, Ill.) approximately every 6 h during the day. Dwell times of as long as 10 h were used overnight.

Drug formulation and administration. Vials containing a dry-fill powder blend of cefepime dihydrochloride and L-arginine were supplied by the Pharmaceutical Product Development Department, Bristol-Myers Squibb Pharmaceutical Research Institute, Syracuse, N.Y. Each 1-g vial was reconstituted with 2.8 ml of preservative-free sterile water for injection; this provided a total volume of 4.1 ml of solution containing 250 mg of cefepime per ml. For the 1,000-mg dose level, 6 ml of the reconstituted solution was mixed with 69 ml of sterile saline solution to prepare an infusion solution containing 20 mg of cefepime per ml. For the 2,000-mg dose level, 12 ml of the reconstituted solution was mixed with 63 ml of sterile saline solution to prepare an infusion solution containing 40 mg of cefepime per ml.

Each cefepime dose was administered as a constant-rate infusion into a forearm vein by means of a syringe infusion pump calibrated to deliver 50 ml of infusion solution in the 30-min infusion interval.

Sample collection. Approximately 5 ml of heparinized blood was drawn from the contralateral forearm vein of every patient immediately predose (zero time) and at 10, 20, 30, 33, 39, and 45 min and 1, 1.5, 2, 4, 6, 8, 10, 12, 15, 18, 30, 36, 39, 48, 60, and 72 h after the start of infusion. Each blood sample was gently inverted a few times for complete mixing and was then placed in a bath of chipped ice. Within 30 min of collection, each sample was centrifuged at $1,000 \times g$ for 15 min and 5°C to separate the plasma. The plasma samples were transferred to appropriately labeled screw-cap polypropylene test tubes and were stored frozen at or below -20°C .

Samples of dialysis fluid of approximately 10 ml were collected immediately before dosing (zero time) and at 0.25, 0.50, 1, 2, 3, 4, and 6 h after the start of infusion. To ensure that these samples were taken from intraperitoneal dialyzing fluid, 50 ml of dialysate was aseptically withdrawn from the dialysis tubing. This fluid was approximately 20 ml in excess of that volume found to occupy dead space in the dialysis catheter and connecting tubing. After collecting the dialysate sample, the initial 50 ml of dialysate was reinfused into the tubing to refill the dead space. At the time of exchange of this dialysate, its total volume was measured and recorded. For all subsequent dialyses, the total dialysate volume was measured and recorded and a 10-ml dialysate sample was collected at the time of exchange. Exactly 10 ml of each dialysate sample was mixed with 20 ml of 0.2 M sodium acetate buffer (pH 4.25) and frozen in appropriately labeled screw-cap 50-ml polypropylene tubes. The samples were stored at or below -20°C .

Total urine voided over the intervals of 0 to 12, 12 to 24, 24 to 48, and 48 to 72 h after the start of dosing was collected from the patients who were not anuric. The collection vessels were kept refrigerated over each interval when they were not in use. At the end of each interval, the urine sample was mixed and the pH and total volume were recorded. A 3.0-ml portion of the urine sample was transferred to an appropriately labeled 15-ml screw-cap polypropylene tube,

and 6.0 ml of 0.2 M sodium acetate buffer (pH 4.25) was added. These urine samples were frozen and stored at or below -20°C .

Creatinine concentrations in plasma and urine were measured for the determination of CL_{CR} by using a Gilson clinical analyzer system. For each patient, a 12-h CL_{CR} normalized to a 1.73-m^2 body surface area was measured immediately before dosing (-12 to 0 h).

Drug analysis. Plasma and urine samples were analyzed for intact cefepime by using validated high-performance liquid chromatographic assays with UV detection (3). Cefepime was quantitated in buffered dialysate by using the assay conditions for plasma. Quality-control samples were prepared in each biological matrix before initiation of the study to verify storage stability as well as the accuracy and precision of each cefepime assay sequence.

Standard curves of cefepime in plasma and dialysate were linear within the range of 0.5 to $50.0\text{ }\mu\text{g/ml}$, and those in urine were linear within the range of 2.0 to $1,000\text{ }\mu\text{g/ml}$. The lower limit of quantitation of cefepime in each biological fluid was established at the lowest concentration of the standard curves. Quality-control samples that contained known concentrations of cefepime were prepared in each biological fluid prior to the initiation of drug administration at each dose level. A coefficient of variation of consistently less than 9% for the quality-control samples suggests that the assays for cefepime in plasma, dialysate, and urine were accurate and precise. The between-day coefficients of variation for quality-control samples of cefepime in plasma at concentrations of 2.0 ($n = 15$), 40 ($n = 12$), and $140\text{ }\mu\text{g/ml}$ were 9, 9, and 7.4%, respectively, where n is the number of replicates of the quality-control sample. The between-day coefficients of variation for quality-control samples of cefepime in urine at concentrations of 10 ($n = 3$), 500 ($n = 3$), and $1,000\text{ }\mu\text{g/ml}$ were 4.4, 2.1, and 3.2%, respectively.

Pharmacokinetic analysis. Plasma cefepime concentration-versus-time data were evaluated by noncompartmental methods (8, 19). The highest observed concentration in plasma (C_{max}) and the corresponding sampling time were determined. The elimination half-life ($t_{1/2}$) was calculated as $(\ln 2)/b$, where b is the absolute value of the slope of the least-squares regression line for n -terminal datum points. These datum points ($n > 3$) were selected to minimize the mean-square error term for the regression. The area under the plasma concentration-versus-time curve (AUC) and the area under the first moment of the plasma concentration-versus-time curve (AUMC) were calculated by using a combination of linear and log trapezoidal rules. The log trapezoidal rule was used when concentration data were in an exponentially declining phase. The AUC from the last point to infinity was estimated by dividing the last measured concentration by the elimination rate constant. The mean residence time (MRT) in the body was estimated as follows: $\text{MRT} = \text{AUMC}_{0-\infty} / \text{AUC}_{0-\infty}$, where $\text{AUMC}_{0-\infty}$ is the AUMC from time zero to infinity, and $\text{AUC}_{0-\infty}$ is the AUC from time zero to infinity. The MRT equivalent for bolus intravenous administration [$\text{MRT}(\text{i.v.})$] was calculated as follows: $\text{MRT}(\text{i.v.}) = \text{MRT} - (T/2)$, where T is the infusion time (0.50 h). Total body clearance (CL) was calculated as $\text{CL} = \text{dose} / \text{AUC}_{0-\infty}$. The steady-state volume of distribution (V_{ss}) was obtained as follows: $V_{\text{ss}} = \text{MRT}(\text{i.v.}) \cdot \text{CL}$. The amount of intact cefepime excreted during each collection interval was calculated as the product of the concentration in the corresponding buffered urine sample and the total volume of urine voided in that interval. Total urinary recovery was calcu-

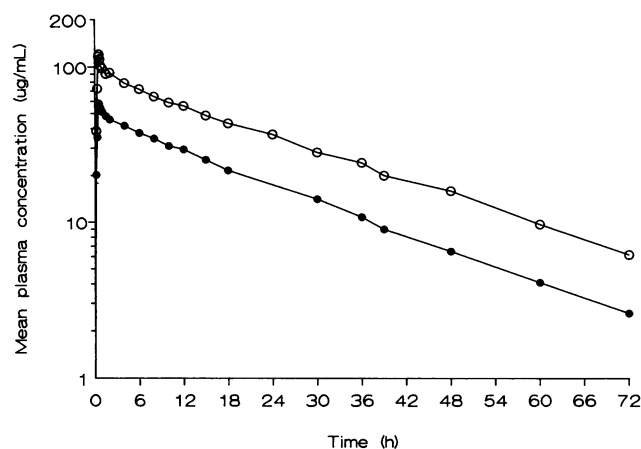


FIG. 1. Mean plasma concentration-versus-time profiles of cefepime following 1,000-mg (●) and 2,000-mg (○) intravenous doses to patients undergoing CAPD.

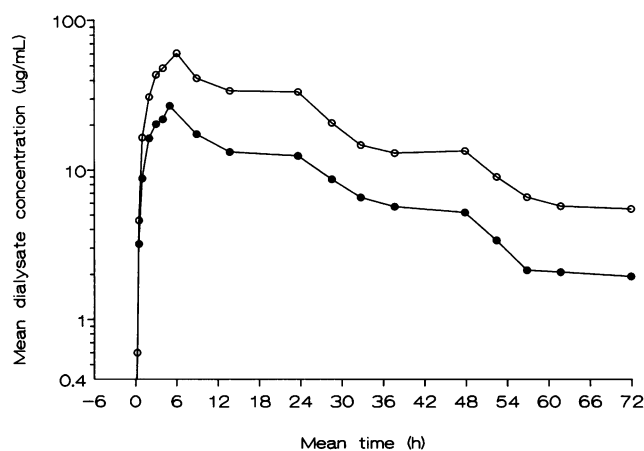


FIG. 2. Mean dialysate concentrations of cefepime following 1,000-mg (●) and 2,000-mg (○) intravenous doses.

lated as the cumulative amount excreted within the collection period and was expressed as a percentage of the administered dose. The renal clearance of cefepime (CL_R) was calculated as $CL_R = X_u/AUC_{0-\infty}$, where X_u is the amount of cefepime excreted in urine.

The amount of intact cefepime excreted in peritoneal dialysate during each dialysis interval was calculated as the product of the concentration in the corresponding buffered dialysis fluid sample and the total volume of dialysis fluid recovered at the end of that interval. The total amount of drug recovered from dialysis fluid was calculated as the cumulative amount excreted within the 72-h collection period and was expressed as a percentage of the administered dose. Dialytic clearance of cefepime (CL_D) was calculated as $CL_D = X_D/AUC_{0-\infty}$, where X_D is the amount of cefepime excreted in dialysate.

Statistical analysis. The mean values of the pharmacokinetic parameters between the two dose level groups were compared by using the two-sample t test. The variances of the two samples were tested for equality by a two-sample F test. If the variances had been found to be unequal, the Welch t test would have been used instead of the usual two-sample t test. All statistical analyses were tested for significance at the $P = 0.05$ level.

RESULTS

Safety and tolerance. There were no abnormal laboratory values related to cefepime therapy; the abnormal values observed were consistent with the prestudy values and were consequences of patient renal impairment. The drug was well tolerated by each patient.

Pharmacokinetics. Mean plasma cefepime concentration-versus-time profiles following administration of the 1,000- and 2,000-mg doses are shown in Fig. 1. The penetration of cefepime into the peritoneal cavity was rapid. The average concentrations of cefepime were 8.8 and 16.5 $\mu\text{g/ml}$ 1 h after administration of the 1,000- and 2,000-mg doses, respectively. The maximum concentrations of cefepime in peritoneal dialysate, 27.0 and 60.7 $\mu\text{g/ml}$, were observed 6 h after intravenous administration of the 1,000- and 2,000-mg doses, respectively (Fig. 2). Over the 72-h observation period, about 25% of the administered dose was excreted into the peritoneal dialysis fluid. Less than 5% of the dose was recovered in urine as intact cefepime.

Pharmacokinetic data for individual patients and their mean values by dose group are given in Table 1. The values for C_{\max} and AUC for the 2,000-mg dose group were twice as high as those observed in the 1,000-mg dose group. The $t_{1/2}$ of cefepime was about 18 h in patients undergoing CAPD and was independent of the dose. The V_{ss} of cefepime was about

TABLE 1. Pharmacokinetics of cefepime in patients undergoing CAPD following single 1,000- and 2,000-mg doses

Dose (mg)	Subject no.	C_{\max} ($\mu\text{g/ml}$)	MRT (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ ($\mu\text{g} \cdot \text{h/ml}$)	CL (ml/min)	CL_R (ml/min)	CL_D (ml/min)	V_{ss} (liters)
1,000	1	51.9	24.6	17.2	991	16.8	0	4.34	24.8
	2	77.6	24.6	16.7	1,245	13.4	0.89	3.50	19.8
	3	75.7	21.6	15.4	1,177	14.2	1.50	4.35	18.4
	4	68.1	28.6	22.6	1,691	9.9	0.10	3.01	17.0
	5	41.1	20.6	16.0	724	23.0	2.50	4.11	28.4
Mean \pm SD		62.9 \pm 15.8	24.0 \pm 3.1	17.6 \pm 2.9	1,166 \pm 356	15.4 \pm 4.9	1.00 \pm 1.04	3.86 \pm 0.59	21.7 \pm 4.8
2,000	6	140	27.2	19.2	2,563	13.0	0	4.00	21.2
	7	120	28.0	19.4	2,495	13.4	0.12	5.14	22.5
	8	107	28.4	20.4	2,202	15.1	0.29	4.54	25.7
	9	115	25.0	16.2	2,151	15.5	0.61	3.36	23.2
	10	135	25.6	18.9	2,611	12.8	0.20	4.72	19.7
Mean \pm SD		124 \pm 14	26.8 \pm 1.5	18.8 \pm 1.6	2,405 \pm 213	14.0 \pm 1.3	0.24 \pm 0.23	4.35 \pm 0.69	22.5 \pm 2.8

22 liters and was independent of the dose. The values for CL and CL_D were approximately 15 and 4 ml/min, respectively, and no dose dependency was observed for the clearance estimates.

DISCUSSION

All 10 patients in this study were in end-stage renal failure that required dialysis and could be regarded as a relatively homogeneous group. The values for V_{ss} in the patients in the present study were almost identical to those observed in previous studies of cefepime in subjects with normal renal function (1, 2) and various degrees of renal insufficiency (4, 5). The data that we obtained in the present study support and extend the findings of the previous studies, namely, that renal impairment does not affect the distribution of cefepime in the body.

As a route of elimination of systemically administered cefepime, CAPD appears to be a less efficient process than hemodialysis. The CL_D of cefepime in the present study was about 9% of that reported for patients on hemodialysis (4). If it were necessary to remove cefepime from the body as rapidly as possible, as in the case of overdosage, hemodialysis should be used.

The CL_D of cefepime (about 4 ml/min) is higher than those reported for ceftizoxime (3 ml/min), ceftriaxone (0.69 ml/min), cefoperazone (0.55 ml/min), and cefotaxime (1.7 ml/min) and is similar to that reported for ceftazidime (9–11, 14, 22). It is expected that antibiotics with larger CL_D values would have relatively higher concentrations in dialysis fluid. The bacteria that are commonly found to cause peritonitis in patients undergoing CAPD (24) and the susceptibilities of these bacteria to cefepime (13), stated as the MIC for 90% of strains tested, are as follows: *Staphylococcus epidermidis*, 0.5 µg/ml; *Staphylococcus aureus* (penicillinase producers), 1.9 µg/ml; *Streptococcus* spp., 0.05 µg/ml; *Escherichia coli*, 0.2 µg/ml; and *Pseudomonas aeruginosa*, 7.0 µg/ml. For at least 48 h after a 2,000-mg dose, the mean concentrations of cefepime in dialysate at the end of each dialysate interval exceeded the MICs for 90% of these bacteria.

For treatment of systemic infections in patients with normal renal function, cefepime is administered two or three times a day. If the dose administered in patients undergoing CAPD is the same as that used in patients with normal renal function, the dosing interval (τ) in patients undergoing CAPD can be calculated by using the following equation: $\tau_c = CL_{(r)} \cdot \tau_r / CL_c$, where the subscripts r and c are for the values in patients with normal kidney function and patients undergoing CAPD, respectively.

By using the mean values for CL in patients undergoing CAPD (14.7 ml/min) and individuals with normal renal function (130 ml/min) and an 8-h dosing interval in patients with normal kidney function, a dosing interval of 70.7 h is calculated for patients undergoing CAPD. This calculation is supported by the observation that, for the 1,000-mg dose, the cefepime levels in plasma at 72 h in patients undergoing CAPD in the present study and at 8 h in individuals with normal renal function (2) are similar. Therefore, for the treatment of systemic infections in patients undergoing CAPD, a cefepime dosage once every 72 h at a 1,000- or 2,000-mg dose level would maintain levels of drug in blood equivalent to those with dosing once every 8 h in patients with normal renal function.

The present study was carried out in patients undergoing CAPD but who did not have peritonitis. Peritoneal transfer of some antibiotics (12) and some endogenous substances

such as urea and creatinine (20) may be altered in the presence of inflamed peritoneal membranes during peritonitis. The clinical relevance of a possible alteration in the pharmacokinetics of cefepime, a cephalosporin with a wide therapeutic margin, in patients with peritonitis undergoing CAPD is questionable. However, further studies of cefepime in patients with and without documented peritonitis undergoing CAPD may be necessary to characterize the effects of peritonitis on the pharmacokinetics of cefepime following an intraperitoneal dose.

Results of the present study suggest that cefepime is safe and well tolerated in patients undergoing CAPD. A parenteral dose of 1,000 or 2,000 mg every 48 h would maintain therapeutic levels of cefepime in plasma and peritoneal fluid for the treatment of systemic and intraperitoneal infections caused by susceptible bacteria, but it would not cause an excessive accumulation of the cephalosporin.

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